IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Appln No. 10/617,038 Confirmation No. 5215

Applicant: Andersen et al

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Examiner: Swartz, Rodney P.

Docket No. SSI5AUSA

Customer No. 00270

Title: Therapeutic TB Vaccine

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Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION PURSUANT TO 37 CFR 1.132

Sir:

I, Peter Andersen, residing at Sparresholmvej 47, DK-2700 Brønshøj, Denmark, do declare and state that:

1. I am a named co-inventor of the present invention. I received my degree in Veterinary science from Copenhagen University in 1988 and my Doctor of Medical Science degree in 1996. I was appointed as Professor in Immunology at Copenhagen University in 2006 and am currently vice president of Vaccine Research and Development at the Statens Serum Institute.

2. I understand that this Declaration is being used to support the arguments that Horwitz, US Patent No. 5,108,745 [*Horwitz*] is not enabling for the claims drawn to a method for producing human vaccine against *Mycobacterium tuberculosis*. Further,

this Declaration is being used to support arguments that Horwitz, US Patent No. 5,108,745 does not teach or suggest a therapeutic vaccine against tuberculosis as defined in the claims of the captioned application, which comprise polypeptides upregulated or expressed during the latent stage of the mycobacteria infection.

3. The full organism name "*Mycobacterium tuberculosis*" is found only in the claims of the Horwitz patent and nowhere else in the document. In the claims reference is made to a vaccine having at least one extracellular product of *Mycobacterium tuberculosis* which stimulates strong cell mediated immune responses in at least one mammalian host infected with or immune to *Mycobacterium tuberculosis* [claim 13]. The dependent claims further recite that the extracellular product is *Mycobacterium tuberculosis* major extracellular protein [claim 14, 16]. Nowhere else in the document is this language found. Nor are there any examples relating to *Mycobacterium* in the specification.

4. In the specification of the Horwitz patent, it is stated that the immunization method involves utilizing extracellular products from intracellular pathogens as immunizing agents [col. 3, lines 55-60]. Given this description, one skilled in the art would conclude, at best, that the vaccine products described by Horwitz would be produced and secreted from the bacilli during an active infection. Conceptually there is no link between secreted proteins (that are characteristic for the logarithmically growing bacteria) and products upregulated in a low oxygen environment (characteristic for the dormant non-replicating bacteria). Further adding to the different nature of secreted and low oxygen proteins, the molecules upregulated under low oxygen may be found in all subcellular compartments of the bacteria. As described in the Horwitz specification, intracellular pathogens such as the Mycobacterium are sequestered within cells of the host organism and not readily detectable by the immune system, se page 2, column 3 line 7-12. The subject of the Horwitz patent is a vaccine based on extracellular

(secreted) protein in contrast to surface exposed proteins, see page 2, column 4, line 16-22. Importantly, although the secretion of extracellular proteins is a continual process the composition and relative quantity of proteins in the mixture of secreted antigens (the so called secretome) is very different when comparing exponentially growing and dormant/non-replicating mycobacteria (J.Bacteriology 2002, 184(13):3485-3491 & Tuberculosis 2004;84(3-4):218-27). Many of the major proteins expressed extracellularly during the exponential growth phase are absent or downregulated during the latent/dormant phase.

5. Review of the Horwitz file wrapper indicated that a Rule 132 Declaration was submitted. This Declaration contained information on which extracellular protein from the M. tuberculosis that Horwitz identified namely a 68 kDa protein. He explicitly states that this "was the only protein visible on a coumassie stained gel". A search of his later publications all relate to a vaccine based on the 30 kDa and 32 kDa major secretory proteins. These proteins were later named the Antigen 85-complex e.g. Ag85B and Ag85A respectively. During the early '90ties the world wide recognised most important extracellular protein, ESAT6, was discovered (US 5955077) and later followed a handful of STCF proteins (WO 9844119); proteins secreted in a Short Term Culture Filtrate. All of these extracellular proteins have been the subject of extensive research aimed at developing a prophylactic TB vaccine. The rationale for this focus was the observation that proteins secreted from the bacterium serve as targets for the immune system at an early stage of infection or during the active infection. Horwitz patent therefore contains no teaching of a vaccine containing any of the amino acid sequences recited in the claimed invention. Knowledge of the polypeptides upregulated or expressed during the latent stage of the mycobacteria infection was first discovered and disclosed with the present invention and later published in J.Bacteriology 2002, 184(13):3485-3491 by the inventors and where the setup for identifying said polypeptides was explained. These polypeptides have a potential for use as a therapeutic vaccine, a vaccine used after the

individual has been infected with TB. This aspect is nowhere disclosed or mentioned in the Horwitz patent as it was not recognized as a possibility at that time.

6. As a person signing below, I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issues thereon.

Name: Date: 27/1-09